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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/455,683 05/31/95 BELL

G ARCD:177/WIM

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HM22/0302

EXAMINER

LANDSMAN, R

ART UNIT

PAPER NUMBER

1646

26

DATE MAILED:

03/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/455,683

Applicant(s)

BELL ET AL.

Examiner

Robert Landsman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- 1) ☒ Responsive to communication(s) filed on 20 December 1999.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 47-52, 63-67 and 83-114 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 47-51, 53-59, 63, 65-67, 81 and 83-114 is/are rejected.
- 7) ☒ Claim(s) 52, 64 and 82 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) _____.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 14) ☒ Notice of References Cited (PTO-892)
- 15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 17) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 18) ☐ Notice of Informal Patent Application (PTO-152)
- 19) ☒ Other: *Sequence Comparison A*.

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DETAILED ACTION

- A. The one month extension of time, filed 12/20/99, has been entered into the record.
- B. Amendment D, filed 12/20/99, has been entered into the record.
- C. The substitute declaration, filed 12/20/99, has been entered into the record.
- D. All 35 U.S.C. Statutes not cited in this Office Action can be found cited in full in a previous Office Action.
- E. The prosecution summary is as follows: claims 1-46 have been cancelled and claims 47-80 have been added by Preliminary Amendment (Paper No. 3). Following a Restriction Requirement claims 47-73 and 75-80 were elected. Claims 53-58, 60-62 and 68-80 were withdrawn from consideration as non-elected species and claims 81-90 were added (Paper No.17). Claims 91-114 were later added (Paper No. 21). Therefore, Group I, claims 47-52, 59, 63-67 and 81-114, are pending in the current application. Applicants have elected this Group without traverse.
- F. Since Applicants are no longer claiming priority under 35 U.S.C. 119(a-d), a certified copy of Application PCT/US94/05747, as required by 35 U.S.C. 119(b), is not required. Instead, Applicants claim priority under 35 U.S.C. 120.

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1. Claim Rejections - 35 USC § 112, second paragraph

G. The rejection of claims 47, 84, 91 and 97 has been withdrawn in view of Applicants' arguments stating that (1) usefulness is not a proper basis for a rejection under section 112, second paragraph and (2) that one in the art would be able to distinguish which type of opioid receptor was binding to a candidate substance.

H. The rejection of claims 47 and 59 has been withdrawn in view of Applicants' arguments that (1) "a polypeptide...selected from the group consisting of:..." is acceptable claim language.

I. The rejection of claims 59, 103 and 109 has been withdrawn in view of Applicants' arguments that one skilled in the art would clearly understand the phrases "composition comprising..." and "specifically interacts." In addition, these claims were amended to remove the term "candidate." These claims are now clear with regard to "said substance."

However, claims 59, 103 and 109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The previous Action also states that the assay does not enable distinguishing between agonists and antagonists and that both of these compounds can bind the receptor. The Action concludes that it is not predictable from the results of the assay that the ligand is an agonist or antagonist and, for this reason, the claims are incomplete as method claims for determining that the substance is an agonist of a kappa opioid receptor. Applicants need to add steps to discriminate between the binding of an agonist and an antagonist.

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J. The rejection of claim 63, 66 and 85-90 has been withdrawn in view of Applicants' amendment to the claim.

2. Claim Rejections - 35 USC § 112, first paragraph

✓ K. The rejection of claims 47 and 59, which requires exposing a test substance to a *plurality of receptors* in which the previous Action alleges that Applicants are not enabled for "a mixture of chimeric opioid receptor polypeptides, or a mixture of recombinant opioid receptor polypeptides, has been withdrawn in view of Applicants' arguments that the application discloses experiments and assays that allow one of skill in the art to screen for and isolate opioid receptor polypeptide ligands.

✓ L. The rejection of claims 47-51, 59, 63, 66, 81 and 83-114 as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention is maintained. Furthermore, claims 65 and 67 has been included as part of this outstanding rejection.

✓ Claims 47, 48, 50, 51, 59, 63, 65-67 and 84-114 stand rejected for the reasons already of record on pages 4-8 of the office Action mailed 8/13/99. The Action of 8/13/99 states that the second extracellular loop of the kappa opioid receptor having the amino acid sequence as set forth in SEQ ID NO:2 or 12 is required for ligand binding and that the claims as they stand do not require an opioid receptor polypeptide comprising at least the second extracellular loop of a kappa opioid receptor encoded by SEQ ID NO:1 or 11. Applicants argue this point stating that they cannot be required to limit their claims to preferred embodiments of their invention. The rejection of these claims is maintained since

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there is a lack of guidance and working examples showing that any portion of the kappa opioid receptor of SEQ ID NO:2 or 12 which does not contain the second extracellular loop would bind ligand. Without this guidance it is not predictable to one of ordinary skill in the art, and would, therefore, require undue experimentation, to make a kappa opioid receptor chimera lacking this domain which binds kappa ligands.

The Action also alleges that the claims are not enabled since the specification does not teach whether 10 amino acids of SEQ ID NO:2 or 12 are sufficient for ligand binding. Applicants argue that, based on the disclosure, one of skill in the art could subclone portions of the kappa receptor into chimeric molecules to test ligand binding. As stated above, there is a lack of guidance and working examples showing that any portion of the kappa opioid receptor of SEQ ID NO:2 or 12 which does not contain the second extracellular loop would bind ligand. Without this guidance it is not predictable to one of ordinary skill in the art how to make a kappa opioid receptor chimera lacking this domain which binds kappa ligands.

Furthermore, since SEQ ID NO:2 is 380 amino acids long and SEQ ID NO:12 is 295 amino acids long, undue experimentation would be required to determine which segment(s) of *at least* 10 amino acids would be sufficient to bind kappa opioid ligand. George et al. (1988; p. 145) states that: "Sequence-comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood." Additionally, Rudinger (1976; especially the Conclusion) states that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." In other words, if a sequence of 15 amino acids binds ligand it is not predictable that shorter or longer peptides would bind the ligand.

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✓ The previous Action alleges that SEQ ID NO:11 does not contain the second extracellular loop of the human kappa receptor and is, therefore, not enabled. Applicants argue that, since amino acids 167-228 of SEQ ID NO:11 *are identical* to the amino acid sequence for the second extracellular loop of the mouse kappa opioid receptor, SEQ ID NO:11 contains the second extracellular loop. Therefore, this rejection has been withdrawn in view of Applicants' arguments. In addition, the previous Action states that the specification does not teach what the complement of SEQ ID NO:1 or 11 encodes. Applicants amended the claims to remove reference to a "complement." Therefore, this rejection has been withdrawn.

✓ The previous Action states that the claims recite the use of a polypeptide encoded by a nucleic acid that is encoded by, or complementary to 30 contiguous nucleotides of SEQ ID NO:1 or 11. Applicants argue that one of skill in the art would appreciate that SEQ ID NO:11 encodes a functional polypeptide by itself or could be used as a portion of a chimeric polypeptide. Applicants' arguments have been fully considered, but are not deemed persuasive.

Claims 47, 59, 84, 91, 97, 103 and 109 encompass a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11. There is no discussion in the specification as to which groups of 30 nucleotides will translate into a functional opioid polypeptide which can bind ligands. Furthermore, random sequences of 30 nucleotides would encompass sequences of nucleotides which do not encode amino acids and, therefore, polypeptides and the specification does not provide any guidance, or working examples of how it is known which of these nucleotide sequences would encode polypeptides. The claim of "at least 30 contiguous bases" also encompass sequences which are larger than 30 nucleotides. Again, the predictability is low as to which of the numerous possible sequences would encode for an opioid receptor polypeptide with ligand binding activity. To determine which groups of 30 contiguous amino acids of SEQ ID NO's:1 or 11 would produce a functional opioid receptor would require undue experimentation.

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In addition, claims 47, 59, 84, 97 and 109 discuss a method of screening using at least 30 nucleotides of SEQ ID NO:11. However, SEQ ID NO:11 is only a partial genomic sequence of a human opioid receptor. Action contends that the claims recite the use of a polypeptide encoded by SEQ ID NO:11, but it is not predictable that SEQ ID NO:11 encodes either a functional receptor or the second extracellular loop of the human kappa opioid receptor, which is thought to be essential for ligand binding. Even if the entire SEQ ID NO:11 was used it is still not clear as to what peptide is encoded for by a *partial genomic* sequence. Furthermore, SEQ ID NO:11 encodes SEQ ID NO:12, which is a partial amino acid sequence. Applicants argue that the human kappa opioid receptor polypeptide sequence disclosed in the specification has significant homology with the mouse amino acid sequence spanning from amino acids 87-380. These sequences, however, are not identical. The possible effect of changing even one amino acid in a polypeptide can be seen in Cunningham and Wells (1989; Abstract) in which certain single substitutions of alanine in various positions of human growth hormone dramatically altered its binding affinity for the human growth hormone receptor. In addition, George et al. (1988; p. 145) states that: "Sequence-comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood." Additionally, Rudinger (1976; especially the Conclusion) states that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study."

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Claims 47-51, 81 and 83-102 are directed toward a method of screening a substance for its ability to interact with an opioid receptor. The previous Action points to the preamble as not directed to determining whether a substance interacts with a specific opioid receptor.

First, the Examiner agrees with the previous Action in that the claims do recite "any" opioid receptor. The claims refer to a process *using* an opioid receptor polypeptide "selected from the group consisting of (1) chimeric opioid receptor polypeptides, (2) recombinant opioid receptor polypeptides encoded..." but does not state that these ligands will *specifically bind* these said chimeric or recombinant peptides. This part of the rejection for claims 47, 84, 91, 97 can be overcome by amending the claims to: 'A process of screening a substance for its ability to interact with an opioid receptor, as defined by subsequent step (a), said process comprising the steps of:..." and changing part (b) of these claims from "contacting said substance with the opioid receptor polypeptide; and" to "contacting said substance with said opioid receptor polypeptide; and."

The previous Action alleges that claim 59, 103 and 109 are not clear as to what compounds are present in the composition used to determine kappa agonists. Applicants argue that one of skill in the art would be able to isolate the compound from the composition based on its binding capabilities. The rejection is withdrawn in view of Applicants' arguments.

However, claims 59, 103 and 109 are rejected since it is not understood how it is known that an opioid receptor polypeptide which comprises at least 30 nucleotides of SEQ ID NO:1 or 11, regardless of whether or not it includes the second extracellular loop of the kappa opioid receptor which has been disclosed as necessary for ligand binding, would be representative of the opioid receptor of SEQ ID NO:1 with regards to determining which ligands are kappa opioid agonists. If these 30 nucleotides are part of a chimeric opioid receptor containing mu and/or delta opioid receptors, or do not contain the second extracellular loop of the kappa opioid receptor, it is not understood how it can be concluded that this

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agonist *at the chimera* will be an agonist at the intact kappa receptor. Again, the possible effect of changing even one amino acid in a polypeptide can be seen in Cunningham and Wells (1989; Abstract) in which certain single substitutions of alanine in various positions of human growth hormone dramatically altered its binding affinity for the human growth hormone receptor. Claims 51, 64 and 82 are objected to since they depend from rejected base claims.

In summary, Applicants have not provided working examples of sequences of 30 nucleotides and/or 10 amino acid peptides which would result in functional opioid receptors, nor have they provided any guidance of how to predict which nucleotide sequences and/or amino acid sequences would code for said receptors, or how to predict binding domains other than the second extracellular loop of the kappa receptor. In addition, the breadth of the claims is too large with regard to the number of possible chimeric opioid receptors. For these reasons, the Examiner has concluded that undue experimentation would have been necessary to one of ordinary skill in the art at the time the invention was made to make and use recombinant opioid receptors comprising at least 30 contiguous bases of SEQ ID NO:1 or 11. Undue experimentation would also be necessary to produce chimeras of opioid receptors which were able to be expressed and maintain opioid receptor function.

3. Claim Rejections - 35 USC § 102

M. The previous Action states that Ahmed et al. anticipate the methods of claims 47, 59 and 84-114. Applicants state that since Ahmed et al. does not teach each aspect of the claimed invention, the rejection is not valid. The rejection of claims 47, 59 and 84-114 has been withdrawn in view of Applicants' arguments. However, the following new grounds of rejection under 35 U.S.C. 102(e) has been added:

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

N. Claims 47, 84, 86, 88, 90 and 97-101 rejected under 35 U.S.C. 102(e) as being unpatentable by Evans et al. Evans et al. disclose (U.S. Patent 5,985,600) an opioid receptor which is 100% identical to 245 contiguous bases of SEQ ID NO:11 (see Sequence Comparison A). Evans et al. also disclose a method of expressing this polypeptide in a host cell (column 14, lines 15-32), screening a substance for its ability to interact with an opioid receptor and a method to detect this interaction (column 7, lines 53 through column 8, line 21 and column 8, line 42 through column 9, line 21).

Claims 48-51, 81-83, 85, 87, 89, 102 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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4. Claim Rejections - 35 USC § 103

O. The previous Action alleges that it would have been obvious to modify the ligand binding assay of Evans et al. (Science, vol. 258, 1992) by using a chimeric delta opioid receptor obtained by replacing a portion of the delta opioid receptor with that of the somatostatin receptor, as taught by Frielle et al. Applicants argue that there is no motivation to combine Frielle et al. with Evans et al. The rejection of claims 47 and 48 has been withdrawn in view of Applicants' arguments.

However, the following new grounds of rejection under 35 U.S.C. 103(a) has been added:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

P. Claims 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. (U.S. Patent number 5,985,600), further in view of Frielle et al. (1988). Claims 48-51 are drawn to a process of screening a substance for its ability to interact with an opioid receptor chimera which comprises at least 30 contiguous bases of SEQ ID NO:11. Evans et al. teach an opioid receptor which is 100% identical to 245 contiguous bases of SEQ ID NO:11. Evans et al. also disclose a method of expressing this polypeptide in a host cell (column 14, lines 15-32) and screening a substance for its ability to interact with an opioid receptor (column 7, lines 53 through column 8, line 21 and column 8, line 42 through column 9, line 21). Evans et al. do not teach the production of opioid receptor chimeras, or a process of screening a substance for its ability to interact with an opioid receptor chimera.

However, Frielle et al. do teach the production of chimeric G protein-coupled receptors (p 9495 under "Construction of Chimeric $\beta 1/\beta 2$ -Adrenergic Receptors") and the use of these chimeras in binding assays. The motivation for producing and using chimeric kappa opioid receptors would be that it is a very efficient method of determining the ligand binding domains of a receptor. It would have been obvious to the skilled artisan at the time the invention was made to modify the ligand binding assay of Evans et al. by using chimeric kappa opioid receptors produced by the method of constructing another G protein-coupled receptor chimera, as taught by Frielle et al. for the prior art recognized benefit of producing an efficient method of determining the ligand binding domains of a receptor.

Q. Claims 59, 63-66 and 109-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. (U.S. Patent number 5,985,600), further in view of Liggett et al. (1993). Claims 59, 63-66 and 109-113 are drawn to a process of screening a substance for its ability to interact with an opioid receptor chimera which comprises at least 30 contiguous bases of SEQ ID NO:11. Evans et al. teach an opioid receptor which is 100% identical to 245 contiguous bases of SEQ ID NO:11. Evans et al. also disclose a method of screening a substance for its ability to interact with an opioid receptor (column 7, lines 53 through column 8, line 21 and column 8, line 42 through column 9, line 21). Evans et al. do not teach the production of opioid receptor chimeras, or a process of screening a substance for its ability to act as an agonist of a kappa opioid receptor chimera.

However, Liggett et al. do teach the production of chimeric G protein-coupled receptors (p. 3666 under "Methods:Constructs") and the identification of agonists at these chimeras. The motivation for producing and using chimeric kappa opioid receptors would be that it is a very efficient method of determining the agonist binding domains of a receptor.

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It would have been obvious to the skilled artisan at the time the invention was made to modify the functional assay of Evans et al. by using chimeric kappa opioid receptors, produced by the method of constructing another G protein-coupled receptor chimera, and identifying agonists to this receptor, as taught by Liggett et al. for the prior art recognized benefit of producing an efficient method of determining the agonist binding domains of a receptor.

It would have also been obvious to one of ordinary skill in the art at the time the invention was made to isolate the substance which interacted with the opioid receptor when screening a library of compounds for the prior art recognized benefit of identifying compounds which interact with the kappa opioid receptor for potential academic, or therapeutic benefits.

Advisory information

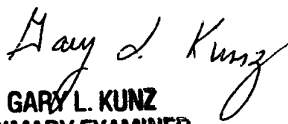
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 25, 2000


GARY L. KUNZ
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